ORIGINAL ARTICLE

Evaluation of Absorbed Dose Estimation Accuracy in Post Radioiodine Therapy for Differentiated Thyroid Disease: A Comparative Study

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ABSTRACT

Introduction: Various amounts of the administered radioiodine dose in differentiated thyroid treatment may expose unnecessary radiation to the inner organs. Hence, accurate estimation of dose to a sensitive organ such as red bone marrow should be accurately determined. This study aimed to determine the accuracy of dose estimation in red bone marrow using three different methods, i.e OLINDA/EXM 2.0, IDAC- Dose 2.1, and EANM method for ^{131}I dosimetry. **Method:** A series of whole-body scans were performed on the twenty-four low-risk patients (17 female and 7 male) who had a total thyroidectomy and received average radioiodine activity of (3304 ± 382 MBq) that range from 2959 to 4045 MBq. For this, manual venous blood sampling of 2 ml was collected at several time points for generating the time-activity curves. Absorbed doses delivered to the red bone marrow were calculated using three different methods. **Results:** Although the identical residence time value was used as an input in the absorbed dose calculation for red bone marrow, the value given by OLINDA ranged from 128 mGy to 674 mGy while IDAC gives a value of 130 mGy to 680 mGy. For the EANM method, the absorbed dose values were ranging from 141 mGy to 725 mGy. **Conclusion:** From the results presented it can be concluded that OLINDA and IDAC show relatively good agreement while the EANM method showing an overestimation of absorbed dose compared to the two methods.

Keywords: Differentiated Thyroid Disease, SPECT/CT, Internal Dosimetry

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INTRODUCTION

Thyroid cancer is becoming more common, and it is expected to become the fourth most common cancer worldwide (1). Increases in the incidence of thyroid cancer can be caused by dietary effects (iodine consumption), environmental causes (radiation and nitrates) as well as comorbidities (chronic lymphocytic thyroiditis) (2). Typically, there are four types of thyroid cancer namely papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), medullary thyroid cancer, and anaplastic thyroid cancer. The most common type of thyroid cancer is differentiated thyroid cancer (DTC) which includes papillary and follicular histology (3).

Thyroid cancer is commonly treated with one or a combination of treatments. Most patients with DTC will undergo surgery whether to remove a small affected part or the entire thyroid gland which is known as near-total or total thyroidectomy and this will be followed by radioiodine (RAI) therapy. Radioiodine therapy has been proven to be an effective method in the treatment of patients with differentiated thyroid cancer after thyroidectomy (4-6). If a low dose of radioiodine ^{131}I is orally administered, it is absorbed into the blood and accumulated in the thyroid gland, which starts to destroy the cells of the gland.

Serum thyroglobulin (Tg) levels can be an indicator to reflect the "burden of cancer" at diagnosis, as well as to determine the efficacy of surgery, to track recurrence and disease progression before and after cancer treatment (7). Several studies (8-10) have shown the clinical benefit of measuring serum Tg (either stimulated or non-stimulated TSH) obtained after total thyroidectomy and before radioiodine administration can assist in early risk stratification and additional therapeutic decision-making. TSH level > 30 mIU/L was commonly implemented in preparation for RAI therapy but there is controversy about the optimal amount of TSH associated with long-term outcome progress (11). Initial clinical work has shown that TSH level > 30 mIU/L is needed to significantly accumulate ^{131}I in incompletely resected

thyroid tumors.

Radiation risk assessment for RAI patients involves internal radiation dosimetry to obtain organ absorbed doses and maximum tolerable activity. Bone marrow seems to be the most radiosensitive tissue and generally the radionuclide therapy dose-limiting tissue (12). Blood-based dosimetry was introduced by Benua *et al.* (13) and they proposed a method of measurement of the acceptable blood dose as well as of the target dose per unit of the activity administered. They reported that radioiodine treatment is safe as long as the dose to the blood is less than 2 Gy and the retention of the entire body at 48 hours is less than 4.4 GBq (120 mCi).

Medical Internal Radiation Dose (MIRD) S factor (mean absorbed dose per unit cumulative activity) was the most common approach to internal radionuclide dosimetry. The MIRD S factors have been estimated from the mathematical simulation of a reference man, but their scale, shape, and location differ greatly from individuals. OLINDA/EXM, which stands for Organ Level INternal Dose Assessment/EXponential Modeling is a computer program written in the Java programming language created by Michael Stabin (14). OLINDA which uses MIRD methodology is an upgrade of MIRDOSE, a program for calculating internal radiation dose estimation in nuclear medicine.

The International Commission on Radiological Protection (ICRP) methodology is another approach used to calculate the absorbed doses. The internal dosimetry computer system, IDAC-Dose 2.1, was built based on ICRP-specific absorbed fractions and computer internal dose assessment frameworks given in ICRP Publication 133 for adult reference (15). The European Association of Nuclear Medicine (EANM) has issued a standard operational procedure (SOP) for pre-therapeutic dosimetry I: blood and bone marrow dosimetry in differentiated thyroid cancer therapy. This guideline using MIRD formalism is intended to assist practitioners on how to customize the therapeutic activity to treat DTC in such a manner that the absorbed dose does not reach a commonly accepted limit for bone marrow toxicity of 2 Gy (16).

OLINDA is a commercial dosimetry software that was approved by the FDA. It is using a voxel-based computational phantom developed by the RADAR group. The absorbed dose calculation is based on the assumption of a uniform distribution of activity in source organs and uniform energy absorption in target organs, which is one of the software's limitations (17). In comparison to OLINDA, IDAC is a free research tool that uses the ICRP 110 adult computational voxel phantom. OLINDA offers a variety of model options, including human and animal models. IDAC, on the other hand, only has two phantom models: adult male phantom and adult female phantom.

The EANM method calculates the red bone marrow absorbed dose using the Sgouros' blood model, with the S value linearly scaled to the patient's total body weight. Thus, this method is more reflective of the actual radiation burden. Since the initial distribution of iodine ions is much greater than that of monoclonal antibodies, the Sgouros' model cannot easily be converted to radioiodine therapy (16). This study aimed to evaluate the accuracy of dose estimation to red bone marrow using blood-based methods in three different tools, ie OLINDA/EXM 2.0, IDAC- Dose 2.1, and EANM SOP for ^{131}I dosimetry.

MATERIALS AND METHODS

Clinical studies

Twenty-four low-risk patients who have undergone total thyroidectomy have received radioiodine activity ranging from 2959 to 4045 MBq (3304 ± 382 MBq). Each selected patient was free from any local or distant metastases. The demographic data for each subject is represented in Table I. Ethical committee approval and informed consent from all patients was obtained. Seventeen patients have discontinued thyroid hormone replacement medication (L-thyroxine) at least 3 to 4 weeks before admission. The remaining seven patients received recombinant thyroid-stimulating hormone (rhTSH). Both groups of patients (group (a) are patients with discontinued L-thyroxine and group (b) consists of patients given rhTSH) are advised to keep to a low iodine diet such as iodized salt, dairy products, egg yolks, seafood, seaweed and kelp products, commercial bread, milk chocolate, iodide-containing multivitamins and soy proteins for at least two weeks before radioiodine treatment. Following administration, patients were isolated for 5 days while their radiation levels decayed to acceptable levels (<50 μSv/hr) (18) for discharge using Geiger Muller (GM) counter. In our department's current practice, patients are encouraged to drink at least 2 to 3 litres of water daily, and the amount of fluid consumed is recorded in the patient's folder. Increased fluid intake has always been recommended to facilitate ^{131}I urinary excretion; therefore, fast whole-body clearance results in a lower absorbed dose (19).

Blood sampling

Blood samples (about 2 ml) were collected at 2, 24, 48, 72, and 90 hours post ^{131}I administration based on EANM guidelines (16). Patients were informed not to excrete urine within two hours after radioiodine administration. Micturition is mandatory for subsequent blood sampling. The activity concentration in the blood was counted in a well counter immediately after the blood sampling. The actual volume of the blood sample was then determined by measuring the weight difference between the entire tube filled with blood and an empty tube by using the

Table I: Patients demographic data.

Study number	Sex (F/M)	Age (Years)	Height (cm)	Weight (kg)	TSH (mIU/L)
1[a]	M	75	170	65	60.5
2[b]	M	61	164	80	82.1
3[a]	F	37	154	63	> 100
4[b]	M	49	173	68	> 100
5[a]	F	33	161	92	62.2
6[a]	F	60	152	46	> 100
7[a]	M	68	166	84	76.2
8[a]	F	67	144	47	83.8
9[a]	F	51	151	69	74.9
10[a]	F	57	166	99	> 100
11[b]	F	34	157	59	> 100
12[a]	F	41	159	74	76.9
13[a]	F	52	150	78	73.0
14[a]	F	50	152	68	78.8
15[a]	F	19	169	81	> 100
16[a]	F	38	158	76	31.7
17[b]	M	29	172	90	> 100
18[a]	F	26	159	56	> 100
19[a]	F	20	156	49	> 100
20[b]	F	52	159	64	> 100
21[b]	M	44	166	76	> 100
22[a]	M	69	163	77	95.0
23[a]	F	31	164	68	45.1
24[b]	F	62	147	66	> 100

[a] group of patients with discontinued L-thyroxine
[b] group of patients given rhTSH

weighing scale.

Well counter versus dose calibrator calibration

To determine a calibration factor (CF) between dose calibrator and well counter, a simple cross-calibration experiment was performed using a small activity of ^{131}I is diluted in different concentrations. The measurement of activity with concentration differences will be plotted on the graph and the slope of the graph represents the CF. To get an absolute activity value, all readings need to be multiplied by the CF.

The activity of RAI was prepared using an Atomlab 200 dose calibrator (Biodex Medical Systems, Inc., New York) while the CRC ® -55tW well counter (Mirion Technologies (Capintec), Inc., USA) was used to quantify the activity in patients' blood.

Whole-body scan

Whole-body scan was performed after two hours of administration and subsequently at 24, 48, 72, and 90 hours. Anterior and posterior whole-body scans were obtained at 15 cm/min scan speed with body contouring mode using a dual-head gamma camera equipped with a high-energy (HE) collimator (Siemens Symbia Intevo Bold, USA). Acquisition parameters have been configured as follows: 364 keV energy photopeak, 15% window width, and matrix size of 256 x 1024. The calibration factor for the camera sensitivity was determined using a known activity of ^{131}I measured accurately in a dose calibrator and with the time of the measurement recorded. The source was placed 10 cm from the HE collimator and was acquired for 100 seconds.

Curve fitting

All the obtained data (activity concentration of the blood and whole-body activity) versus time were plotted using MATLAB (version R2020a, The Math Works, Inc., Natick, MA) computation on mono and bi-exponential fitting graph. The time intervals between whole-body scanning and blood sampling are to generate the time-activity curve (TAC) for dosimetry. The area under the curve (AUC) from TAC will provide information about accumulated activity inside the patient's blood thus will be used to calculate the residence times.

Absorbed dose calculation

Dose Estimation software

In radioiodine therapy, the absorbed dose to the blood is mainly caused by beta radiation originating from activity in the blood. Two dosimetry software i.e. OLINDA/EXM 2.0 and IDAC-Dose 2.1 were used to calculate the absorbed dose of the red bone marrow in this study. To measure the absorbed dose, we determine the residence times (τ_{blood}) for the concentration of activity in the blood by integrating the respective retention function from zero to the maximum time point (90 hours), and then the calculated residence time was entered in OLINDA and IDAC to obtain the absorbed dose.

EANM method

By using the EANM method for ^{131}I dosimetry, the absorbed dose for red bone marrow was calculated using the given equation:

$$\frac{D_{redmarrow}\,(Gy)}{A_0(GBq)} = 61 \times \tau_{blood}(h) + \frac{0.106}{Patient\ body\ weight(kg)} \times \tau_{total\ body}(h)$$

To obtain the residence time of the whole-body activity ($\tau_{total\ body}$), we integrated whole-body retention from zero to maximum time point.

Ethical clearance

This study was approved by Human Research Ethics Committee USM (USM/JEPeM/19080465) and Medical Research & Ethics Committee, Ministry of Health Malaysia (NMRR-19-2075-49016 (IIR)).

RESULTS

Patient study

Among twenty-four patients, there were seven patients with TSH reading less than 30 mIU/L for whom was given intramuscularly (IM) thyrogen (rhTSH) to stimulate the TSH values before being administered for RAI therapy. The remaining seventeen patients have discontinued thyroid hormone replacement medication for 3 to 4 weeks before admission.

Figure 1 illustrates the fitted bi-exponential activity concentration curves of patients with discontinued L-thyroxine and patients given rhTSH. As shown in Figure 1, all the curves show a decreasing trend of the blood samples activities with time. The area under the curve in Figure 1 indicates the cumulative activity for all categories of patients. The accumulated activity was seen to be lower in patients receiving rhTSH than in patients with discontinued L-thyroxine.

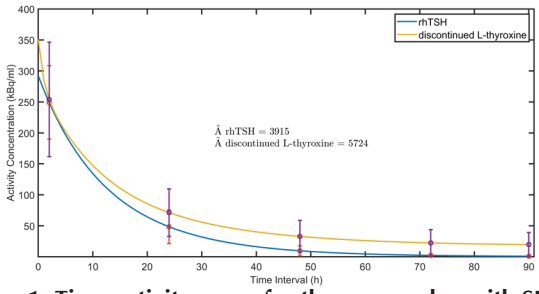

Figure 1: Time activity curve for the mean value with SD bar of whole blood activity concentration over (a) seventeen patients with discontinued L-thyroxine and (b) seven patients that are given rhTSH.

Figure 2 show the estimated absorbed dose for red bone marrow generated by the OLINDA, IDAC, and EANM method for two groups of patient (a) and (b). It was demonstrated that the value given by both software i.e OLINDA and IDAC does not show any difference. The mean activity encountered in all patients of group (a) is 3345 ± 407 MBq compared to group (b) is 3202 ± 317 MBq. While the activity was approximately the same in both groups, absorbed dose measurements indicated that rhTSH group was lower than the discontinued L-thyroxine group. According to the measurement of both OLINDA and IDAC, red bone marrow absorbed doses following therapy did not vary substantially from

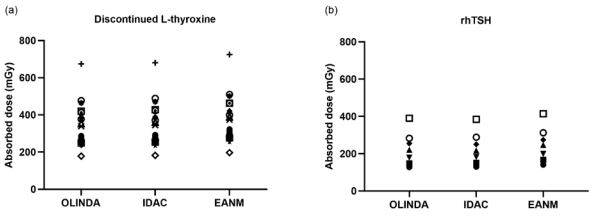

Figure 2: Absorbed dose estimated for different dosimetry approaches over (a) group of patients with discontinued L-thyroxine and (b) group of patients that are given rhTSH. Each symbol representing an individual subject.

each other with the maximum difference of 2.5%. Meanwhile, using EANM dosimetry techniques, it was observed that the percentage difference of absorbed dose readings was ranged between 6.1% and 12.7% compared to the OLINDA calculation.

Pearson Correlation Coefficient was used to test for linear relationships between the three datasets. Figure 3 shows a strong positive correlation between IDAC and OLINDA, with a correlation coefficient of 0.9993, and a correlation coefficient of 0.9989 between EANM and OLINDA. Both lines that represent the line of identity have an R-squared value of 0.9979.

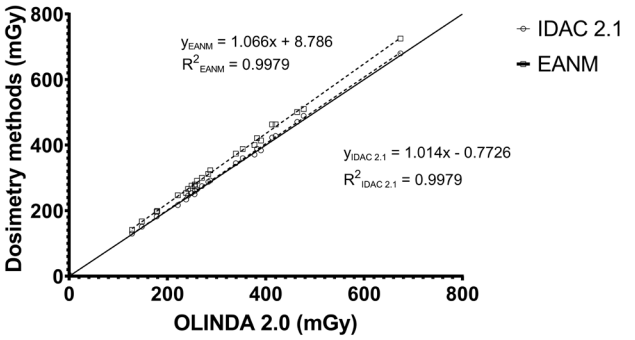

Figure 3: Scatter plot of various dosimetry methods (IDAC and EANM) against OLINDA as a reference. The solid line represents the line of identity (LOI).

DISCUSSION

There is no difference when comparing the two methods for calculating absorbed dose, using OLINDA and IDAC. MIRD approach used in OLINDA calculate the absorbed dose to the organ through radioactive damage to the source organ. While the ICRP techniques in IDAC are based on expanding evaluations of biological effects caused by ionizing radiation.

Both tools allow modification of input data, such as masses of organs. The default value for organ masses in each software shows that there are different values between them. Although we have set the same mass values for both software and the same residence time value, the readings that we obtain for the red bone marrow absorbed dose were still different. This is probably due to the varied internal dosimetry model used in both software where ICRP model modifications are influenced by developing risk assessments of ionizing radiation biological effects.

In this study, the absorbed dose of red bone marrow calculated by IDAC and OLINDA did not differ significantly with a maximum difference of 2.5%. The different values obtained may be due to the differences in the arithmetic mean of male and female organ-specific weighting factors. The acquisition of a large number of activity-time data points is often not feasible in clinical practice. Divergence in absorbed dose readings among

patients with approximately the same administered activity is probably due to a change in the biokinetics of the individual patient.

When comparing the two software, IDAC that uses ICRP methodology remains consistent with the definition of the absorbed dose, and the improvement of the model is guided by an expanded assessment of the biological effects of ionizing radiation. Since this approach is defined for radiation protection purposes, the underlying kinetic data represent a healthy population (20).

Compared to the calculations made using the EANM method, it was found that the absorbed dose estimations were slightly higher than the calculation by OLINDA and IDAC. This is probably due to the overestimation of $\tau_{\text{total body}}$ in EANM method. The EANM technique takes into account the patient's weight as well as whole-body retention throughout the maximum time point i.e. in this study the maximum time point is 90 hours.

To get a significant effect of radioiodine therapy, adequate thyroid-stimulating hormone (TSH) stimulation for radioactive ^{131}I administration, both for imaging and subsequent ablations, is recommended for the management of differentiated thyroid cancer. The most common approach to achieve this goal is endogenous TSH stimulation by discontinuing L-thyroxine. Many studies (21-23) have reported comparable results as the traditional withdrawal of thyroid hormone with recombinant human thyroid-stimulating hormone (rhTSH) intervention.

Two different groups of patients treated for RAI were present in this study; (a) a group of patients with discontinued L-thyroxine for three weeks prior to treatment and (b) a group with two rhTSH injections prior to ^{131}I therapy.

In the rhTSH group, excretion of ^{131}I from the body was faster compared to the thyroid hormone withdrawal group regardless of dose calculation methods (24, 25). Technically, the faster excretion rate of ^{131}I from the body will impact on the reduction of the dose to whole-body and will also beneficial in the improvement of the whole-body image quality due to low background activity.

The two lowest absorbed doses for all three methods can be seen in the two patients with rhTSH injections. In fact, this is expected to coincide with the study conducted by Pacini et a.l (22) stating that patients treated with rhTSH obtained improved quality of life and had lower radiation exposure to the blood compared to the discontinued L-thyroxine group of patients.

CONCLUSION

MIRD and ICRP internal dosimetry-based models are found to be in agreement with small deviation when using the absorbed dose concept. The general principles of the ICRP and the biological effect of ionization radiation influence specific model formulations. Both tools managed to provide an accurate estimation of an absorbed dose to the red bone marrow for subjects with thyroid hormone withdrawal or using rhTSH. The EANM method involves blood and whole-body counts that are monitored for different levels of radioactivity. The calculation of the absorbed dose using the EANM method was influenced by the individual patient mass and body counts. This study highlights an overestimation of absorbed dose in EANM method compared to the other two methods. OLINDA and IDAC show relatively good agreement in estimating red bone marrow absorbed dose in post radioiodine therapy for DTC. Further validation needs to be performed in estimating individual organ's absorbed dose based on 3D image-based with OLINDA and IDAC.

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